THE NEW HYGIENE

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THREE LECTURES

ON THE

PREVENTION OF INFECTIOUS DISEASES

BY

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With a Preface by E. RAY LANKESTER

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PREFACE

On the New Hygiene, or the Prevention of Infectious Diseases.

IT is no small pleasure to me to be associated with the publication of my friend Metchnikoff's Harben Lectures—and I am much honoured by being asked to write a preface to this little book.

It is a wonderful and exceptional thing: for here we have the statement of one of the greatest investigators of disease, in the fullness and ripeness of his work and knowledge, placing before the general reader some of the latest results in regard to infection, the part played by those peculiar vegetable organisms—the infective germs or bacteria—the part played by the eater-cells or phagocytes of man when attacked by such germs, and again

telling us as to the dangers to civilised mankind of allowing parasitic worms to harbour in his alimentary canal. In the third lecture some of the latest knowledge with regard to the terrible and preventable malady known as Syphilis is set forth in a spirit at once truly scientific and truly philanthropic.

These lectures will be read with interest and advantage by medical men, and also by the layman. It is right that intelligent men and women who have not a medical training should follow, so far as they are able, the progress of the warfare waged by such men as Metchnikoff against disease. And it is an immense advantage that they should derive their information on this subject from a great original discoverer, and not from the exaggerated or incomplete gossip of newspapers.

Anyone who has a moderate acquaintance with elementary physiology, such as is taught in many schools nowadays, though not in those frequented by the children of the wealthy, can follow Dr. Metchnikoff's exposition and enjoy the admirable method in which he establishes his views by citation of most convincing observations and experiments.

Even to the well-read medical man these pages will furnish much novel matter of first-rate importance, accompanied by reference to the special publications of recent investigators, many of whom are pupils of the "Institut Pasteur."

Although working for the last twenty-five years in Paris in the great Pasteur Institute for the study of disease, surrounded by medical colleagues and medical pupils, Elias Metchnikoff began his career and attained great distinction as a naturalist — more especially an investigator of the cellular embryology or growth from the egg of the lower animals. He was led to his fundamental views on the scavenger-like activity of the amœboid or colourless protoplasmic corpuscles of the blood and tissues (to which he gave the name "phagocytes") by his investigation of the transparent young of marine organisms and the actual observation of the ingestion and digestion of parasitic germs by "phagocytes," which belonged to the blood of a water-flea, and could be seen in the living animal by means of the microscope.

As appears not infrequently in these lectures, Dr. Metchnikoff is a philosopher with definite

conclusions as to the value of scientific knowledge to the well-being of man. His book on "Human Nature" is a most original and entertaining series of illustrations of man's failure, as yet, to harmonize himself with his necessary natural conditions. His treatise on "Inflammation" and that on "Immunity" are scientific works of the highest originality and importance.

These lectures should be regarded by the reader as a brief gaze into the mind and mode of work of one of the greatest living men of science,—a true benefactor of his race but above all an enquirer, filled with the consuming ardour of the *Curiosi Naturæ*.

E. RAY LANKESTER.

THE NEW HYGIENE

I.

THE HYGIENE OF THE TISSUES

HAVING been invited by the Council of The Royal Institute of Public Health to deliver the Harben Lectures, I must first of all thank them very sincerely for the great honour they have conferred upon me. With regard to the subject of these lectures, I have thought that it would interest you to hear some reflections on the conditions which may insure our health. Following the request of your President, I have chosen three subjects which are intimately connected with the work on which for nearly a quarter of a century I have been engaged.

The latter half of the past century has been remarkable for the extraordinary progress made by the science of medicine. Whilst formerly the views held on the causes and origin of infectious diseases were most vague, they have in recent times become well defined under the influence of Pasteur and his school. As soon as we had discovered the pathogenic microbes, an effective fight against many diseases became possible. Although therapeutics have gained many most important victories, yet to hygiene belongs without a doubt the place of honour in modern medicine. It is in the prevention of infectious diseases that the interest of medical art is now mainly centred. But, whereas formerly all preventive measures were based on insufficient and often erroneous knowledge, they nowadays are founded on truly scientific data. How great is the difference between the measures at present employed against the propagation of plague, of cholera, and of yellow fever, and those in use before the micro-biological era of hygiene! Modern precautions are far more simple and incomparably more effective than the old-time ones. Instead of troublesome and useless quarantines, instead of blindly distributing disinfectants, we now endeavour to

lay our hands on the actual sources of contagion, and to destroy the animals conveying it, be they rats, mosquitoes, or the like.

With the progress of medical science hygienic measures have become more and more precise, thus rendering ever better and more effective services to mankind. Many of these measures aim at the destruction of the pathogenic microbes outside of the human body, because it is feared that should they once find their way into it they will most surely cause disease. For a long time the ideal of hygienists has been to preserve man from all contact with the germs of infection, just as one was wont to preserve organic matter by placing it out of the reach of microbes. It was not until later that it was recognised how exaggerated was this ideal, which in practice often presented the greatest difficulties. It is not even correct to say that inert organic matter remains unaltered only so long as no bacteria are present. Thus, in acid organic liquids, such as infusions of herbs or urine, microbes may exist without causing any fermentative changes, provided that these microbes are such as can only grow on neutral or alkaline media. Thus also organic matter containing

anaerobic germs remains unchanged so long as it is exposed to the air.

Far oftener we meet with cases where the living body remains intact, in spite of its containing pathogenic microbes. Not very long ago quite the contrary was thought to be the case. When Loeffler first found diphtheria bacilli in the throat of a healthy child, doubts arose in his mind as to the etiologic rôle of his microbe. At that time hygienists endeavoured to prove that the infectious agents were regularly present in diseased, and absent in healthy persons. Latterly it has become generally acknowledged that a man may be the host of diphtheria bacilli, cholera vibriones or other pathogenic bacteria, without necessarily developing the corresponding diseases. Experimental work has confirmed and amplified these results. Thus, it was proved to be possible to introduce quantities of tetanus spores into the body of a guinea-pig without the animal, which is exceedingly prone to develop tetanus, acquiring the disease. But Vincent has shown that by placing it under unfavourable conditions—*e.g.*, by exposing it to too high a temperature—its resistance can be overcome and tetanic symptoms be produced.

All these results could not fail to influence practical hygiene. Until a short time ago we were convinced that the principal, if not the sole, cause of outbreaks of typhoid fever lay in drinking-water. Every effort was therefore made to keep the drinking-water supplies free from typhoid bacilli in the hope that thus enteric fever might be exterminated. Yet there have not been wanting examples of persons who acquired this disease although they never drank water, or drank only boiled water, and who never ate raw food. The bacteriological work carried out during the past few years in this connection has at least partly helped to solve the mystery.

The fact is that perfectly healthy persons, especially such as have come in contact with typhoid fever patients, or with persons who have suffered from enteric at a more or less remote period, often harbour the *Bacillus typhosus* in considerable numbers in their alimentary canal. Such persons have been termed "bacilli carriers" (*Bacillenträger*), and must be considered as important sources of infection for this disease.

These bacilli carriers have been found at all ages—from children of eighteen months to old

men of sixty. I will take from a recent paper by Dr. Kayser,[1] of Strassburg, some details as to this very important subject.

A woman of forty years of age, proprietress of a bakery in Strassburg, suffered from typhoid fever ten years ago. In the last few years she was struck by the fact that almost all her employés and apprentices, soon after entering her service, began to suffer from more or less grave digestive troubles. One of them contracted a very severe attack of typhoid, and died in the third week of his illness. About a year after, a second fatal case of enteric occurred in another employé of this bakery. These occurrences aroused the suspicions of the medical officer, and he raised the question whether the woman might not be a carrier of *Bacilli typhosi*. Bacteriological examination of her fæces fully confirmed this suspicion; it was proved that she often excreted a great number of *Bacilli typhosi*. This fact readily explained the infection in persons who were in the habit of taking their meals at the baker's shop, whose food was prepared by the proprietress herself, and who had to use the same closet as herself.

[1] *Arbeiten a. d. Kais. Gesundheitsamte*, 1906, vol. xxiv. p. 176.

The woman, however, showed nothing abnormal, with the exception of an enlargement of her liver.

This fact must interest us as affording proof of the power of typhoid bacilli to retain their virulence for many years in a body unaffected by their pathogenic action. As these microbes were found to be present in the contents of the alimentary canal, they must often have had the opportunity of finding their way into the tissues, carried thither through some little wound produced by a piece of bone or some other sharp body. Yet such penetration of the bacteria remained without effect, and the woman continued to enjoy perfect health by reason of the immunity conferred on her by her former attack.

Now, what reason can be given for this remarkable and prolonged immunity?

According to the idea of many scientists who have studied this question, the woman owed her resistance to certain changes which the fluid part of her blood had undergone during the original attack of typhoid fever. Her blood-serum at that time had acquired the capacity of agglutinating typhoid bacilli in clumps and of destroying them by a humoral

action. In fact, an examination of her serum made during the mortal illness of one of her employés proved that it agglutinated typhoid bacilli in a dilution of 1 in 100.

In the course of an attack of typhoid fever there is formed in the serum, at the same time as the agglutinating substance, a property called "sensitizer"—*i.e.*, a substance which modifies the typhoid bacilli in such a way as to render them more liable to be destroyed in the body. The idea that these properties of the body liquids play a primary rôle in immunity has become so deeply rooted that it has even been suggested to measure the degree of immunity by the agglutinating or the sensitizing power of the blood-serum. At a later stage, however, it became necessary to give up this method. I will now state some facts which may throw light on the problems in question.

Besides those bacilli carriers who are resistant to the disease, and whose body liquids possess the above-mentioned properties, others are occasionally met with who have, more or less, completely lost them. Thus, in Strassburg, a lady was found to be a typhoid-bacilli carrier twenty-four years after having had an attack of enteric fever. She was, therefore, refractory to

the disease, and yet her serum possessed no higher agglutinating power towards typhoid bacilli than the serum of any normal person.

A second example I will take from the essay of the well-known Japanese bacteriologist Shiga.[1] Twelve years after an attack of typhoid fever he examined his blood-serum, and found it to be quite devoid of any agglutinating or sensitizing properties. Yet Shiga had not lost his immunity, as we shall see later on.

Now, whereas, on the one hand, persons may be refractory to typhoid fever, without possessing any specific properties in their body liquids, yet, on the other hand, the presence of such properties in no way guarantees immunity. Thus you may frequently observe a large quantity of these agglutinating and sensitizing substances in the serum of patients at the time when a relapse of the disease is preparing. For this reason Widal, the inventor of the sero-diagnostic method of typhoid fever, has always maintained that these properties are no indicators of a refractory state of the body. Recently, Jürgens[2] observed a typhoid fever patient who had a relapse about two months

[1] *Berliner Klin. Wochenschrift*, 1904, No. 4.

[2] *Berliner Klin. Wochenschrift*, 1905, p. 141.

after his first attack. This relapse occurred in spite of his serum possessing marked agglutinating and sensitizing properties. By reason of this observation, Jürgens concludes that, "in spite of the normal development of agglutinins and bactericidal substances, immunity could not have been produced, and that there must, therefore, be other causes which induce the refractory state."

What might these other reasons be? A careful study of some similar examples will enlighten us on the subject.

After having proved that his serum contained no agglutinin, Shiga injected himself subcutaneously with liquid products of the *Bacillus typhosus*. He found that already after eight days the agglutinating power of his serum was manifest in a dilution of 1 in 640; the sensitizing substances showed a corresponding increase in the same space of time. The serum of another person, who was injected with the same substance, showed an agglutinating power only in a dilution of 1 in 80 after the same interval. This great difference—for Shiga's serum agglutinated eight times more strongly than the other man's—may be explained by the fact that the Japanese bacteriologist had had

typhoid fever twelve years before, whilst his colleague had never suffered from the disease.

Shiga's immunity, therefore, consisted in a vital modification of his cellular elements, as was proved by the overproduction of agglutinins and sensitizing substances.

As we have here touched upon one of the essential points of immunity, we must consider it more in detail. An experimental research carried out by Cole[1] has shown that immunized rabbits, after having completely lost their agglutinating power, regained it very rapidly after having received a fresh injection of typhoid bacilli. The same phenomenon was, therefore, observed in these animals as in Shiga, viz.—that during immunization there was produced an important modification of certain cells which have acquired the property of reacting very intensely to the introduction of typhoid bacillary substances into the organism.

These facts, together with many similar ones, prove that the essential phenomenon in acquired immunity consists in certain modifications which living parts of the body undergo. It would, therefore, be most important to establish the nature of these elements.

[1] *Zeitschrift für Hygiene*, 1904, vol. xlvi.

Some time ago Pfeiffer and Marx, in their studies on the experimental immunity of rabbits toward the cholera vibrio, proved that the sensitizing substance originates in three groups of organs, namely, the spleen, the bone-marrow, and the lymphatic glands. They believe that these organs acted thus, inasmuch as they were hæmatopoietic organs. Yet it is evident that the secretion of the sensitizing substance can have nothing to do with the production of the red blood corpuscles. Besides, the lymphatic glands, which do not produce these cells, nevertheless prepare the sensitizing substance. It would be more correct to say that this substance is the work of the phagocytic organs, for all of these organs, without exception, contain and produce phagocytes.

The discovery of Pfeiffer and Marx was almost immediately afterwards extended by Wassermann and Takaki to the question of experimental immunity against the *Bacillus typhosus*. In corresponding researches Deutsch-Détre proved that the phagocytic organs are the nuclei of production of the anti-typhoid sensitizing substance. On the strength of all these researches we may conclude that the phagocytes, those cells which fight against the

microbes, which devour and digest them, are able to elaborate and even to excrete into the blood substances which fix themselves on to the microbes and render them more amenable to their destruction by the body.

Recently Wassermann and Citron have published some new researches on the origin of the anti-typhoid sensitizing substance, in which they insist on the local production of these substances. After injection of typhoid bacilli into the peritoneal or pleural cavities of animals, they found the sensitizing substance to be present in the peritoneal or pleural liquid (as the case might be) before it appeared in the blood-serum. From these facts Wassermann and Citron concluded that every living cell could produce sensitizing substances—a conclusion which far exceeds the results of their experiments. The peritoneal and pleural liquids, far from harbouring all sorts of cellular elements, contain a number of different phagocytes, and, therefore, the new experiments of these two authors only give further support to the thesis that the phagocytes are the true producers of sensitizing substances.

Acquired immunity should therefore be regarded as a superactivity of the phagocytes,

which manifests itself by the overproduction of sensitizing substances, by their power of reacting strongly towards the introduction of microbes and their products, and, lastly, by their capacity of enveloping pathogenic microbes, and of destroying them intracellularly.

An extensive series of experiments carried out in the last few years has proved that the essence of immunity lies in the living elements of the body, and that it is the phagocytes which deliver us from our enemies. The humoral theories of immunity, which sought to explain this phenomenon by certain pre-existing properties of the body liquids, have proved to be incapable of accounting for that assertion. But latterly the attempt to detract the importance of phagocytic action by subordinating it to a humoral influence has been renewed. It is chiefly Wright who has made himself the champion of this new theory. Though fully recognising that the destruction of microbes in the organism is mainly effected by the phagocytes, Wright asserts that these cells can only act on such microbes which have already been impregnated with *opsonin*—*i.e.*, a soluble substance circulating in the

blood, and present also in the other body liquids.

As proof of this theory, Wright cites numerous experiments made by himself and Douglas, in which he allowed the phagocytes to act on microbes outside of the human body, *in vitro*. If the mixture of these living elements is bathed in normal serum of man or animals, phagocytosis begins almost immediately, whereas it does not commence until much later, and is but imperfectly accomplished, when phagocytes and microbes are brought in contact with serum that has been heated to 60° C. If the microbes alone are emulsified in unheated normal serum, the opsonin of the serum fixes itself on to them, and makes them amenable to speedy envelopment by the phagocytes. As a result of these observations, Wright supposes that the phagocytes play only a passive rôle, which depends on the preliminary action of the opsonin.

Neufeld and Rimpau[1] of Berlin, have carried out similar experiments, the difference being that instead of studying the action of phagocytosis on normal serum, they worked with the sera of animals immunized against various

[1] *Deutsche Med. Wochenschrift*, 1904.

microbes—streptococci and pneumococci. They also found that in these sera there exists a substance which has no direct action on the phagocytes, but which can fix itself on to the corresponding microbes, and thus modify them in such manner that they are the more easily devoured by the phagocytes. Neufeld and Rimpau call this substance a "bacterio-tropic substance," and consider it to be distinct from the opsonin because it is not destroyed by heating to 60° C.

This question — whether in the sera of normal and of immunized animals there exists one single substance which can fix itself on to the microbes, or whether there are two different substances, opsonin and sensitizing or fixing substance—has given rise to several very delicate researches, which have not yet led to a definite solution. According to the opinion of Dean of the Lister Institute, an opinion which seems most probable to us, in all these substances of the body liquids we have only to do with sensitizing substances. The fact that normal sera after being heated to 60° C. no more favour phagocytosis, whilst the sera of immunized animals preserve this power in spite of heating, might, according to Dean, be

explained by differences in the quantities of the contained sensitizing substances. The normal sera, which only contain a small amount of them, lose their activity after a short heating to 60° C., whilst the sera of immunized animals, being much richer in sensitizing substances, retain a sufficient quantity of them even under such conditions, and do not lose them completely until they are heated to between 65° and 70° C.

In a Paper recently published by Hektoen.[1] the author studied the opsonic action of dog's serum towards anthrax bacilli. This property was lost even by heating to 56° C. But the serum, although thus deprived of its opsonin, yet showed a sensitizing action against the anthrax bacilli. Hektoen therefore leans towards the dualistic opinion which affirms a difference between opsonic and sensitizing substance.

Under these circumstances it becomes impossible to come to a precise conclusion as to the nature of the opsonin. But the scientific data already accumulated will allow us to judge of its rôle.

[1] *Journal of Infectious Diseases*, March, 1906, vol. iii., p. 102.

The experiments of testing a serum for its influence favouring phagocytosis or its opsonic influence are always carried out *in vitro*. Mixtures are prepared of heated or unheated sera with washed leucocytes and microbes. The phenomena of phagocytosis are studied for only a short period, at the end of which the number of bacteria enveloped by the phagocytes is counted and compared with the number of bacteria which have remained free in the liquid outside the phagocytes. The longer the time of observation is extended in this experiment, the more the differences between the effect of heated and of unheated serum tend to diminish. Now, it must be kept in mind that phagocytes do not behave in quite the same manner outside the body as they do in their normal surroundings and under natural conditions. I have repeatedly had occasion to compare the progress of phagocytosis in the peritoneal cavity with that occurring in the peritoneal exudate of the same animal *in vitro*. The differences are often very marked. There can be no doubt that, under such artificial conditions and outside the body the phagocytes are weakened and cannot show their functional activity to such advantage as inside the body.

It is, therefore, quite natural that under such unfavourable conditions the phagocytes more readily attack the microbes already impregnated with preparatory substances than the quite intact microbes; when they have been deprived of this favouring influence the phagocytes can only fulfil their duties with more or less delay. Now, that is exactly what in reality takes place. Left to themselves in a liquid deprived of all opsonic substances, the phagocytes nevertheless surround the microbes; only instead of doing this in a quarter of an hour, it takes them longer, perhaps an hour or two.

In order to obtain more precise data about these phenomena, I requested Dr. Loehlein, of Leipzig, who was at the time working in my laboratory, to carry out a series of experiments on the subject in question. Loehlein has confirmed the principal observations of Wright and Douglas, but he has added some new results, of which I shall have to give you a detailed account, as Loehlein's research has not yet been published.

Loehlein worked with anthrax bacilli, to which were added equal quantities of fresh sera of different animal species—rat, guinea-pig, pigeon, rabbit and mouse. After a certain

interval (forty minutes) he introduced into each of these mixtures equal quantities of washed white blood corpuscles from a guinea-pig. Besides this, he prepared a control mixture containing the same quantities of bacilli and leucocytes, but to which, instead of serum, there had been added normal saline solution. In accordance with Wright's researches, it was found that after fifteen minutes and half an hour there was a great difference between the absorption of bacilli by phagocytes taking place in serum, and that which is observed in normal saline solution. An hour after the beginning of the experiment the quantity of bacilli enveloped by the phagocytes in normal saline solution showed a marked increase; another hour later the differences in phagocytosis disappeared, and the phenomenon became equally marked in normal saline solution as in the different sera.

If it were true that the preparatory or opsonic influence of the sera was of fundamental importance in immunity, one would expect to see it most marked in the sera of the least sensitive animals. But in reality that is by no means the case. Thus in Loehlein's experiments the serum of guinea-pigs, the animals most sensitive to anthrax, had a far higher opsonic

power than that of pigeons, which are much more resistant to anthrax. No parallelism, therefore, exists between immunity and the opsonic action. In Loehlein's experiments the absorption of the bacilli by the phagocytes often occurred quite as early in normal saline solution as in the sera, and thus the importance of the opsonins is still further diminished. It is evident that in those cases where the white blood corpuscles are less seriously affected by the change in their surroundings they will more easily be able to envelop the microbes without the aid of the opsonins.

In my own experiments I took the peritoneal exudate from guinea-pigs vaccinated against anthrax, and isolated the leucocytes from this exudate. These, after being washed in normal saline solution and emulsified in the same liquid, enveloped anthrax bacilli without any aid of serum opsonins. Furthermore, Wright[1] has himself in his later publications acknowledged the occurrence of spontaneous phagocytosis—*i.e.*, phagocytosis which becomes apparent without any addition of opsonins.

One might suppose that in these cases

[1] *Proceedings of the Royal Society*, Series B, vol. lxxvii, No. B. 516, p. 213.

of spontaneous phagocytosis the opsonin, should it really be indispensable, might be secreted by the leucocytes. Thus, these cells having been transferred into normal saline solution, and finding no opsonin in the surrounding liquid, might themselves give off enough of it to allow them to envelop the microbes. This supposition has not yet been experimentally verified, but should it be confirmed it would prove that the phagocytes are capable of producing substances preparatory to phagocytosis. If the opsonins were identical with the sensitizing substances, the problem might be considered as already solved, for, as stated above, the phagocytes are without a doubt one of the sources of these latter substances.

The experimental results which I have just described to you will prove that either the absorption of the microbes, may be effected without the help of the opsonins, or that—should such help be indispensable—the opsonin may be supplied by the leucocyte itself. But even if one were forced to the conclusion that the preparatory action of the opsonins was absolutely necessary, and that these substances could only arise from the serum, their function

would still appear to be a far less important one than that of the phagocytes. For the opsonins can only prepare the microbes for their destruction by fixing themselves on to them, but they are not able to modify these microbes in their vitality or virulence, whereas the phagocytes hinder the microbes from multiplying, kill them, and make them entirely to disappear.

In order to judge of the relative importance of the humoral influence and the phagocytes' action in immunity, one need only recall a certain number of well-established facts. In his researches on acquired immunity towards the cholera vibrio, R. Pfeiffer was much astonished to see his vaccinated guinea-pigs dying in spite of the presence of great quantities of sensitizing substances in their body liquids. These animals died of the infection caused by the cholera vibrio. Now this result can readily be reproduced by paralyzing for a certain time the activity of the white blood-cells. Cantacuzène succeeded in killing by vibrionic infection even highly immunized guinea-pigs by a preliminary injection of small quantities of tincture of opium. Thus it was sufficient simply to retard

the phagocytic action in order to make the animals lose their immunity, and to render them an easy prey to the vibriones. The general bearing of this fact also appears in the analogous experiments of Gheorghiewsky,[1] which were carried out on guinea-pigs vaccinated against the *Bacillus pyocyaneus.*

If we sum up the whole of these observations on immunity against infective agents, we cannot but conclude that this phenomenon is the result of a phagocytic action, that in other words immunity is a function of the cells.

If we see that bacilli carriers in general and the notorious bakeress of Strassburg in particular, can sow the disease broadcast in their surroundings, without themselves falling ill, the reason is, that their living cells react efficiently against the pathogenic microbes and can rapidly produce substances injurious to these microbes.

These results may serve to give us a general rule of hygienic behaviour towards our cellular elements. These cells should be stimulated in their activity, in order successfully to fight the germs of infection. Thus in most of the methods of vaccination against microbial

[1] *Annales de l'Institut Pasteur*, 1899.

diseases a modification of the cells in this sense is being effected. Everything that might weaken the phagocytic action, like the tincture of opium in the experiments mentioned above, should be strenuously avoided.

Although the phagocytes belong to the most resistant elements of our body, yet it is not safe to count on their insensibility towards poisons. We have seen how they are harmed even by small doses of opium. I am not able to enter into details with regard to all the substances which are adverse to phagocytic action, but I must call your attention to the influence of alcohol on immunity.

It is well known that persons who indulge too freely in alcohol show far less resistance to infectious diseases, especially to croupous pneumonia, than abstemious individuals. The vaccinations against hydrophobia carried out on persons bitten by mad animals are almost always successful; but those cases in which the treatment does not stop the outbreak of the disease are most frequently observed in individuals addicted to alcoholism.

In pursuance of this observation, Déléarde,[1] of the Pasteur Institute in Lille, has undertaken

[1] *Annales de l'Institut Pasteur*, 1897, p. 837.

a series of experiments, which have proved to him that the absorption of alcohol is without a doubt a grave obstacle to the immunization against hydrophobia. At the same time he found that rabbits to which he administered alcohol in the course of immunization against anthrax died of this disease, whilst the control animals, which were given no alcohol, could be vaccinated without any difficulty.

Abbot[1] has confirmed these experiments by proving that animals, if subjected to the influence of alcohol, became more sensitive to the harmful effects of several microbes, such as streptococci, staphylococci, and bacterium coli. Later on Laitinen[2] carried out a great number of experiments from the same point of view and with similar results. Our interest centres mainly in his experiments on the vaccination against anthrax. To a number of rabbits alcohol was administered for several days in succession; they were then injected subcutaneously with a small dose of the first vaccine of anthrax. Six animals thus treated died after a more or less prolonged illness; all of these contained anthrax bacilli in their blood

[1] *Journal of Experimental Medicine*, vol. i., p. 447.
[2] *Zeitschrift fur Hygiene*, 1900, vol. xxxiv., p. 206.

and organs. Of four control rabbits which received the same dose of the same vaccine, but to which no alcohol had been administered, only one died, whilst the other three enjoyed perfect health. Several other experiments furnished similar results.

Alcohol therefore suppresses the natural immunity of rabbits towards the first vaccine of anthrax. This impairment of their resistance was manifested by the inactivity of their white blood-cells; thus the bacilli were permitted to multiply without being checked by a sufficiently strong phagocytic reaction. As has been established by Massart and Charles Bordet, the leucocytes are sensitive even to small doses of ethyl alcohol, and present a negative chemiotaxis in the presence of this substance.

Besides its deleterious influence on the nervous system and other important parts of our body, alcohol therefore has a harmful action on the phagocytes, the agents of natural defence against infective microbes.

Some scientists have endeavoured to find out whether alcohol could also influence the production of humoral substances in the immunized organism. The great majority of researches on this question agree on the fact that chronic

alcohol poisoning diminishes the amount of these substances in the blood, whilst, on the other hand, a single dose of alcohol given internally or injected subcutaneously increases the quantity of these antibodies (Friedberger, P. Th. Mueller). Only Carl Fraenkel was not able to confirm the harmful influence of alcohol on their production.

As a logical consequence of the experiments on the weakening of immunity under the influence of alcohol, it has been suggested to eschew this substance in the treatment of infectious diseases. Without wishing to enter into a discussion of this question—for therapeutics do not belong to the scheme of these lectures—we must strongly insist on the danger of alcoholism with regard to the resistance against pathogenic microbes.

But it is not only opium and alcohol which hinder the phagocytic action. A number of other substances regularly employed in medicine cause the same results. Even quinine, the prophylactic effect of which in malarial fevers is indisputable, is a poison for the white blood-cells. One should, therefore, as a general rule, avoid as far as possible the use of all sorts of medicaments, and limit oneself to the hygienic

measures which may check the outbreak of infectious disease. This postulate further strengthens the thesis that the future of medicine rests far more in hygiene than in therapeutics.

Whilst a number of substances weaken the resistance of the body, there exist others which act in the opposite sense.

More than ten years ago it was shown by Issaeff[1] that by injecting guinea-pigs with different liquids—*e.g.*, normal saline solution, urine, serum, etc.—it was possible to increase their resistance towards pathogenic microbes. Animals thus treated supported doses of the virus to which the control animals inevitably succumbed. It was only natural to apply these results, which were confirmed by a great number of observers, to the prevention of infectious disease. Thus Durham suggested the injection of serum during surgical operations.

This plan of enhancing the phagocytic action in general medical practice might, with great advantage, be employed by physicians. The new method is already beginning to find its way into practice, and is worthy of attracting general attention. A Paris surgeon, Raymond

[1] *Zeitschrift für Hygiene*, 1894.

Petit,[1] has, after working at the Pasteur Institute, commenced employing horse serum in certain of his operations. Numerous experiments on laboratory animals had left no doubt as to the efficiency of horse serum in strengthening the body's power of resistance towards infective microbes. In order to render this serum as harmless as possible, he heated it to 55° C. before injecting it. Now, serum alone is an excellent culture medium for all sorts of microbes, and its action against infection cannot be explained on the principle of its being a bactericidal liquid. The favourable influence of the serum can only consist in the fact that it produces a powerful effect on the white blood-cells. After a few hours it causes a marked accumulation of phagocytes, and these in their turn envelop and destroy the microbes, thus preventing them from infecting the body. Control animals—*i.e.*, animals which have received no injection of horse serum—show only an infinitely weaker phagocytic action, and regularly succumb to the infection.

Encouraged by the results of his animal experiments, Petit decided to employ heated

[1] *Annales de l'Institut Pasteur*, 1904; *Revue de Gynécologie et de Chirurgie Abdominale*, 1904, No. 4.

horse serum in his gravest operations. He used it for the first time about five years ago, on a woman on whom he operated for multiple fibromata of the uterus, complicated by inflammation of both annexes and by suppurative pelvic peritonitis. After opening the abdomen, the surgeon found "the pelvis blocked with a mass which extended into the abdomen and occupied both iliac fossæ. The great omentum completely enveloped this mass, and was everywhere adherent to its surface." Under these conditions an operation would have appeared almost impossible. Yet Petit carried it out, taking care to pour into the abdominal cavity, before suturing the abdomen, about 30 grammes of heated horse serum. The result of the operation was most successful. The patient speedily recovered, and we were not a little astonished to see her a few weeks after the operation arriving at the Pasteur Institute on her bicycle.

As it appeared that this most encouraging result was to be ascribed to the serum, Petit has continued making use of it in a series of other abdominal and pleural operations. Several other surgeons have also followed his example, and, as the results have always been

most satisfactory, it is to be hoped that the method will soon come into general use.

Without entering too far into the details of this subject, I should like to mention one example which appears to me to be most convincing. It was communicated to the Académie de Médecine of Paris by Fernet.[1] The case in question was that of a young doctor who was suffering from gangrenous pleurisy. As soon as the pleural cavity had been opened, there welled forth a most fœtid pus containing an enormous quantity of microbes and only very few leucocytes. Two rabbits injected with this liquid died of septicæmia on the next day. For several days after the operation the patient's state showed no trace of improvement, and the pus issuing by the drain-tubes still presented the same appearance. It was therefore decided to inject heated horse serum into the pleural cavity. "The results obtained," says Fernet, "fulfilled all our hopes: every injection was followed by a remarkable change in the liquid excreted by the pleura; whilst before the injection of serum the liquid was teeming with

[1] *Bulletin de l'Académie de Médecine*, October 3, 1905, pp. 186-190.

microbes, and contained only very few leucocytes, on the day after the injection the number of free microbes had notably diminished, and some of them were already enveloped by leucocytes; on the other hand, the leucocytes showed a marked increase. This change for the better became more marked from day to day, so that after the fourth injection, instead of the serous, reddish liquid of the foregoing days, there now issued from the wound only a creamy pus. Microscopical examination showed that this liquid contained innumerable leucocytes enclosing many microbes, whilst only a small number of microbes remained free in the liquid." In spite of the long duration of the illness, its issue has been favourable, and the resistance of the body, reinforced by the injections of serum, has led to a complete recovery.

Besides these experiments carried out in France, the German surgeon, Miculicz, whose loss we all mourn, has also endeavoured to introduce into surgery the use of substances increasing phagocytic reaction. To this end he practised subcutaneous injections of a solution of nucleinic acid twelve hours before the operation. He thus caused an increase in the

number of white blood corpuscles in the blood, which reached as many as 24,000 per 1 cubic millimetre. To my mind, the method of injecting heated horse serum into the peritoneal or pleural cavity is superior to that of Miculicz; but both these methods must be regarded as most useful for protecting the tissues of the body when injured and weakened by operation. Evidently neither the use of serum nor of nucleinic acid are the last words of wisdom. A detailed study of the influence of divers substances for the calling forth of the white blood cells will teach us many new facts that will be of use to us in the hygiene of our tissues. The principle of this hygiene consists in increasing the number and activity of the phagocytes.

In analyzing the mechanism of the influence of horse serum on the post-operative period, we find no difficulty in coming to the conclusion that this influence is not brought about by an increase in the sensitizing substances or by a production of opsonins. Petit has studied the quantity of sensitizing substances present in the peritoneal exudate of laboratory animals, in which the formation of an exudate had been caused by injection of heated horse serum. He

found that in this respect the exudate did not differ from the blood of the same species of animals. With regard to the opsonins, there is no trace of them present in the serum employed for injection, as it has been heated to 56° or 57° C.

The use of substances enhancing the phagocytic reaction in the protection of tissues which are subjected to operation is but the first step forward in the hygiene of the tissues. This subject will have to be extended to other cases where our living organs are threatened by microbes, and where it is necessary to protect the former against the latter. With regard to this question, we may rejoice that the foundation stone of the hygiene of the tissues—*i.e.*, the thesis that the phagocytes are our arms of defence against the infective germs—has at last been generally accepted.

II.

THE HYGIENE OF THE ALIMENTARY CANAL.

In the lecture on the hygiene of the inner tissues of the body which I had the honour of delivering before you, I developed the thesis that on the phagocytes in general, and on the white blood corpuscles in particular, devolves the duty of ridding our body of the microbes and other parasites which try to penetrate into it. In those cases where the intruders succeed in gaining a foothold for any length of time a real battle is fought, necessitating the intervention of a number of leucocytes. Also in infectious diseases their number is increased, and a more or less marked leucocytosis is produced. The exceptions to this rule are very rare—*e.g.*, in typhoid fever and malaria—and even these exceptions are rather apparent than real. In malarial fevers leucocytosis does exist, but it is a passing feature, and must be looked for at an opportune moment. In typhoid fever leucocytosis is not observed at

the time when the typhoid bacilli are multiplying in the blood. In certain infectious diseases, such as croupous pneumonia, the degree of leucocytosis is even frequently employed as a prognostic criterion, for it has been proved that the greater the number of leucocytes, the better are the patient's chances of recovery. In surgical affections, the number of white corpuscles in the blood often gives most valuable indications. Thus, in appendicitis, a disease which we shall consider more in detail later on, leucocytosis may often help us to decide whether surgical intervention is urgently needed or whether it may be deferred or perhaps even avoided.

If on examination of the blood we note a marked increase of the leucocytes, we are wont at once to think of an infectious disease. But there are cases in which leucocytosis sets in normally, if I may say so, quite apart from any disease. Such an occurrence is that of the digestive leucocytosis. Many observers have found that in man, as well as in several other mammals, the number of white blood cells increases some time after meals. There are differences of opinion as to the explanation of this phenomenon, but its existence is admitted

by everyone. In order to gain more precise data, the endeavour has been made to study it by experimental methods in animals. Recently Nicolas and Lot[1] have published an extensive Paper on the subject, in which they have established the fact that in the dog the number of white blood cells rises after a meal, especially if the food consists of raw beef. But it would be a mistake to imagine that leucocytosis is only observed after a full meal. Thus, according to a recent publication of Kier,[2] rabbits show a very marked digestive leucocytosis after having eaten nothing but vegetable food, such as cabbage and bread. The greatest number of leucocytes was found one hour and a half after the meal.

What is the reason for this analogy with the leucocytosis of disease, an analogy so striking that one might be tempted to inquire whether the digestion of food is not also a kind of infection? The fact of the matter is that, after meals, a certain number of microbes penetrate through the intestine, and find their way into the circulation. This question has been much discussed from every point of view, but, as a result

[1] *Archives de Médecine Expérimentale*, 1905, p. 164.
[2] *Nordiskt Medicinskt Arkiv*, 1905, vol. xxxviii., pp. 1-32.

of all these controversial statements, it seems to be proved beyond a doubt that microbes can penetrate into the blood by way of the intestine. In numerous experiments carried out on horses, dogs, rabbits, etc., it has been proved that certain microbes traverse the intact intestinal membranes, and lodge either in the lymphatic glands or in the lungs, the spleen and the liver. The microbes may even be met with in the lymph and blood. Doubts have frequently been expressed whether the intestinal mucous membrane could allow microbes to pass without its having been injured. From a practical point of view this question is not very important, for under natural conditions the wall of the intestine frequently enough has occasion to be injured by sharp or hard particles of food, such as pieces of bone, the stony tissues of certain fruits, etc. In the Pasteur Institute, where great experience on the methods of preparation of therapeutic sera has been gained, we have for years made it a standing rule never to bleed a horse after a meal, because under these conditions the development of microbes may take place in the serum, even if it has been obtained under the strictest aseptic precautions. An animal should always be kept

fasting before being bled, if it is to furnish a sterile serum.

It is highly probable that the microbes of the digestive tract, which multiply abundantly after every meal, find better opportunities of traversing the intestinal wall at this time than at any other period of the day.

The theory of Von Behring—that tuberculosis in man is caused by the ingestion of Koch's bacilli in early childhood—has lately given rise to a great deal of research work on the mode of entry of microbes into the inner organs and the blood by way of the intestine. It has been recognised that the digestive tract is one of the most important entrance-gates for the virus, just as the simplest way of infecting a horse with glanders is to make it swallow glanders bacilli with its food; thus also generalized tuberculosis and even tuberculosis of the lungs are most easily caused by way of the intestine. Recently Calmette and Guérin,[1] as well as Vallée,[2] have published several new data in proof of this assertion. Whilst the direct introduction of tubercle bacilli into the trachea of calves was, in Vallée's experiments,

[1] *Annales de l'Institut Pasteur*, 1905, p. 601.
[2] *Ibid.*, p. 619.

followed only by slight lesions, the absorption of the same bacilli by way of the intestine produced a severe tuberculosis of the bronchial lymphatic glands. It is evident that the development of tuberculosis of the lungs may be ascribed to bacilli which have been swallowed with the food, although these microbes need not produce visible lesions whilst traversing the intestinal wall.

Not all pathogenic microbes, it is true, show so great a power of invading the body from the intestine. Thus, it is most difficult to cause anthrax in guinea-pigs by making them swallow the virus. But the slightest lesion of the intestinal wall is sufficient to enable the swallowed bacilli to enter into the body and to cause a fatal infection.

Many researches have recently been undertaken with the object of finding out whether the intestinal membrane of new-born and of very young animals is more easily traversed by microbes than that of adults.[1] Many of these experiments have given positive results, but it has at the same time been proved that the intestinal mucous membrane of grown up animals is by no means absolutely impenetrable

[1] Ficker, *Archiv fur Hygiene*, 1905, vol. xlix.

to microbes. In the experiments of Calmette and Guérin adult goats were even more prone to acquire tuberculosis of the lungs by way of the intestine than were kids.

Although there still remain several open questions with regard to the mode of infection by way of the intestine, yet no doubt remains as to the very great importance of this gate of entry. It is very probable that in many diseased conditions which one is wont to attribute to intestinal intoxication, an infection of the blood by intestinal microbes, more especially the *Bacillus coli*, has really taken place, these microbes having invaded the body tissues through the walls of the bowels.

The entirety of these results, which have been accumulated by science, prove that the intestinal wall is worthy of being made the subject of most careful hygienic consideration.

Our recently-acquired knowledge of infectious diseases has shown that many of those which were formerly attributed to special miasmata circulating in the atmosphere in reality originate from wounds caused by certain lower animals.

Especially to English investigators science and humanity are indebted for this funda-

mental idea. After the memorable discoveries of Manson on the rôle of mosquitoes in the transmission of filariæ, Bruce has shown that the disease called nagana is caused by a trypanosome which is inoculated through the tse-tse fly, or *Glossina morsitans.*

Since then a large series of Arthropoda have been recognised as dangerous intermediaries which transmit to man and to animals the virus of human plague, of malarial fever, yellow fever, relapsing fever, sleeping-sickness, Texas fever, spirillosis of fowls, etc. Most frequently Diptera, such as mosquitoes and flies, are the transmitting agents. In bubonic plague fleas play the rôle of inoculators, in relapsing fever bugs and ticks fulfil similar functions. Within the last few years insects and Arachnidæ have attracted the most intense interest of medical men and naturalists, and whilst formerly only a few amateurs devoted themselves to the detailed study of the Dipteræ and Arachnidæ, these classes have nowadays become the object of most assiduous study to a great number of scientists.

As a result of these investigations, an elaborate system of hygienic measures—some of them most effective ones—has been worked

out. One endeavours to avoid and to destroy mosquitoes, rats carrying fleas, etc. A most simple hygienic precaution has recently been recommended by Koch against African relapsing fever. According to him, one need only avoid the huts which are infested with ticks and sleep at a certain distance from the road of the caravans in order to avoid this fever.

To the diseases originating from wounds of the skin and caused by Arthropoda correspond the diseases originating from wounds of the intestine and caused by entozoa, mainly intestinal worms. Numerous facts can be adduced in favour of this assertion.

Formerly great attention was given to these parasites, to which were attributed all sorts of local and general maladies. In therapeutic systems of fifty or sixty years ago a great deal was said for vermifugal remedies, by which many intestinal troubles and even certain nervous disorders were believed to have been cured. Since that time the parasitic worms have been removed to a very different plane, and they have been nearly forgotten in favour of the microbes, to which is assigned the place of honour in medicine. The worms were so often seen living quietly in the intestines, and their

hosts were found to be in no way suffering through them, that one had grown accustomed to consider them as almost, or quite, inoffensive. And yet this optimism is by no means justified. There can, of course, be no doubt that an intestinal worm need not impair health in any way, just as many mosquitoes, fleas and ticks may prick man and animals without causing anything more than a transitory and not painful itching. But, on the other hand, it is equally certain that the bites of intestinal worms may cause just as much evil as the pricks of Arthropoda carrying pathogenic microbes. This fact may best be established by a study of appendicitis, that modern and much-talked-of disease.

Not long ago there was brought to the Pasteur Institute a verniform appendix which had been removed by a surgeon from a boy eleven years of age. The operation had been undertaken during a very severe and most characteristic crisis of appendicitis, which was accompanied by very high fever, up to 106·9° F. As happens frequently in operations of appendicitis carried out in the inflammatory stage, the case ended fatally. Inspection of the appendix revealed considerable hyperæmia, and microscopical examination showed a severe inflam-

mation of the mucous membrane, part of which was ulcerated and contained a female Oxyuris. An investigation into this case was undertaken by Dr. Weinberg, and he brought to light the noteworthy fact that the parasite was surrounded by a zone of inflammation, in which was recognised a quantity of white blood cells and a certain number of large Gram-positive bacilli. The explanation of this case is not difficult. An Oxyuris, having penetrated into the appendix, attacked the mucous membrane, and there inoculated a microbe which produced a fatal infection. The rôle of the parasite was, therefore, quite similar to that of a flea which inoculates the plague bacillus to man, and thus causes his death.

Some years ago, and after the attention of medical men had been directed to the importance of intestinal parasites in the etiology of appendicitis, Dr. Girard[1] showed us some histological sections of an appendix that he had removed from a girl during an operation for pelvic peritonitis. The illness had presented no clinical features of appendicitis, but rather appeared to be peritonitis proceeding from the genital organs. In the sections, stained by

[1] *Annales de l'Institut Pasteur*, 1901, p. 440.

Gram's method, a Trichocephalus was observed, which had partly bored itself into the mucous membrane of the appendix. Surrounding the worm was found a layer of leucocytes, among which a considerable number of different bacteria could be seen. These two examples which I have just detailed to you leave no doubt as to the etiologic rôle of the intestinal worms in appendicitis. These parasites injure the wall of the bowels and there inoculate microbes, causing an inflammatory reaction. The number of appendicitis cases in which entozoa, especially Nematodes, are found would appear to be considerable, so far as one can judge from the literature upon this subject.

Nearly forty years ago surgeons called attention to the presence of worms in stercoral abscesses that were accompanied by pains, these abscesses being localized in the region of the cæcum and ascending colon.[1] Since then the presence in the inflamed appendix of entozoa, such as Trichocephali, Oxyures and Ascarides, has from time to time been observed. But these discoveries were looked

[1] *V. Desprès*, "*Traité du Diagnostic des Maladies Chirurgicales*," 1868, *p.* 279.

upon as something purely accidental and devoid of any general importance. The success which frequently results from vermifugal treatment in persons suffering from appendicitis has proved to us the importance of the entozoa in this disease, and that is the reason why I decided five years ago[1] to call the attention of medical men to this subject. Objections to this hypothesis of mine were not wanting. The fact was recalled that the intestinal worms are often found to be present in the digestive tract without causing the slightest trouble there, and the assertion of Dr. Matignon was quoted, that the Chinese harbour many entozoa without ever suffering from appendicitis. Our opponents also insisted on the absence of parasites from a great number of appendices obtained by operation, this absence being confirmed by the negative result of examination of the fæces.

This scepticism could not fail to lead to corresponding results in medical practice. Without entering into any details of cases in my own circle of acquaintances, I will quote but one of the most characteristic examples. The wife of a professor of hygiene, a highly

[1] *Bulletin de l'Académie de Médecine*, 1901, *p.* 301.

distinguished medical man and bacteriologist, contracted appendicitis with classical symptoms. Microscopic examination of the fæces did not reveal the presence of any intestinal worms. The husband deemed it superfluous to carry out vermifugal treatment, as he attached no importance to the rôle of entozoa in the etiology of appendicitis. The patient was, therefore, operated on, and after that everything went on pretty much in the normal way. Some little time after, the husband was attacked with pains in the region of the appendix, and repeatedly presented grave symptoms of appendicitis. This, then, is an example of family appendicitis, of which a certain number of cases has already been published. The patient allowed himself to be operated on during the non-inflammatory period, after having found that his fæces contained no parasites. In spite of the dexterity of the surgeon, the operation was followed by unpleasant complications, which persisted for several months and which caused the patient much anxiety. Now, the examination of the appendix showed the presence of an Oxyuris, which was firmly attached to the mucous membrane. It is very probable that,

had the patient been subjected to vermifugal treatment, and followed the rules of rational hygiene, he would have been cured without any difficulty. It is also probable that the attack of appendicitis in the professor's wife had a similar origin, and that it was the Oxyures which infected her with pathogenic microbes.

Since my early observations on the rôle of entozoa in appendicitis I regularly examined the fæces microscopically, and only suggested the thymol treatment in those cases where I found ova of Trichocephalus or Ascaris to be present. But since it has been proved that appendicitis is frequently caused by Oxyures, which do not lay their ova in the contents of the intestine, it is surely wise to prescribe this treatment in any and every case of this disease. Thus, in the case of a lady who had suffered from a severe attack of appendicitis, and whose fæces appeared to be absolutely free from any kind of ova, but whose husband had harboured Oxyures, thymol treatment was attended by a very good result.[1]

After having caused inflammation in the

[1] *Vide* Hall, *Centralblatt fur Bakteriologie*, Referate, 1904, vol. xxxv., p. 150.

appendix, the parasites frequently leave this organ, and therefore need not be found there at the time of the operation. This would explain certain cases which all were agreed in considering as not caused by worms, because neither entozoa nor their ova had been discovered. The assertion that the Chinese and certain other people belonging to inferior races never suffer from appendicitis, in spite of the frequency with which intestinal worms are found in them, should be accepted with great reserve. It is well known that in China autopsies are very rarely carried out, and that, therefore, the cause of peritonitis cannot easily be discovered. With regard to slight cases of appendicitis, which are by far the most common ones, they surely run their course in China without the assistance of European doctors.

My sceptic attitude towards this question has become even more pronounced since an observation that I made in my own laboratory on chimpanzees. Amongst about fifty of these anthropoid apes, on which autopsies were performed by Dr. Weinberg, five cases of recent or inveterate appendicitis were found. One was especially interesting,[1] as it was a

[1] *Annales de l'Institut Pasteur*, 1904, p. 323.

fatal case of appendicitis which progressed very rapidly, and presented the most characteristic symptoms. In this case intestinal worms were found to be present. But even should it have been proved in an absolutely convincing manner that the carriers of entozoa in China were free from appendicitis, such a fact might yet be easily explained, because this disease occurs only through the intervention of pathogenic microbes. Now, the latter need not be found in the alimentary canal of the Chinese. We see something quite similar in the rôle the Anopheles plays in the propagation of malaria. In order that the bite of this insect should give rise to the fever, it is absolutely necessary that the mosquito be contaminated by the malarial parasite. Now, many Anopheles are not thus infected, and that is the reason why one may very often be bitten by them without contracting the disease.

It is very probable that the rôle of intestinal worms is not limited to the inoculation of the microbes of appendicitis. Dr. Guiard[1] believes that they may also serve to transfer typhoid bacilli to the mucous membrane, and thus to be the cause of enteric fever. This supposition is

[1] *Comptes Rendus de la Soc. de Biol.*, 1901, p. 307.

a very probable one, and it will have to be carefully studied.

The researches of Weinberg[1] on the anthropoid and lower apes have shown that these animals often die of septicæmia caused by *Bacillus coli*, and it is highly probable that the inoculation of these bacilli has been caused by intestinal worms adherent to the wall of the bowels. Even in certain tumors the rôle of the entozoa would appear very probable. It has been repeatedly observed that the presence of Bilharzia in the bladder of man causes there the formation of genuine epitheliomata. More recently Borrel[2] has called attention to the presence of intestinal worms in the centre of tumours of mice, which he believes to be of intestinal origin.

The whole of these data which I have here laid before you indicate that it is high time to undertake a campaign against the entozoa, which would have to be conducted on similar lines to the war now waged against the mosquitoes and other microbe carrying Arthropoda. The difference would be that measures directed against the intestinal worms are far

[1] *Comptes Rendus de la Soc. de Biol.*, 1906, vol. I., p. 446.
[2] *Ibid.*, 1905, p. 710.

more easily carried out in practice. Against the mosquitoes, which fly about in the air, which surprise man during his sleep, and prick him even through his clothing, the fight is often unsuccessful. But in order to hinder the intestinal worms from penetrating into the human body, it suffices as a rule to keep a careful watch over our food-stuffs. It is astonishing to see how often they show contamination by human dejections containing ova of entozoa. By such contamination it is to be explained that so many persons harbour parasites in their alimentary canal. I have already mentioned the example of a professor of hygiene being a carrier of Oxyuris. Other persons living under conditions of ease and affluence are very often attacked by helminthiasis.

Soon after having read before the Académie de Médecine of Paris my paper on the rôle of intestinal worms in appendicitis, I was invited by a surgeon to visit a provincial estate which was remarkable for the frequent occurrence of this disease. In one family four persons had to undergo the operation, and one of them died. Not only members of this family, but also many of their servants, showed the

symptoms of appendicitis, and it had been noticed that a few months' stay on the estate sufficed to cause the disease to break out. It was suggested that the water, which was very rich in lime salts, might be the cause of the disease. After examining the fæces of most of the inhabitants of this estate, I was struck by the frequent occurrence of the intestinal worms Trichocephalus and Ascaris, no attempt being made to count the Oxyures, as their number cannot be estimated from the examination of the fæces. The conclusion was inevitable: the food taken on this estate must often be contaminated by human excreta The luxury in which the inhabitants of the chateau lived, and the apparently irreproachable cleanliness, appeared to contradict this opinion. It was necessary to carry out a minute and detailed inquiry in order to find the key to this problem. The kitchen garden which furnished the vegetables for the inhabitants of the estate was walled in, and altogether left nothing to be desired. But the manure which was applied to the beds of the kitchen garden came from a spot communicating with the servants' closet. The servants' fæces, which doubtless contained entozoa and their ova, were passed on to the

vegetables, and thence into the intestine. The period which elapsed between the time when the fæces left the bodies of the servants and when they were consumed by the masters would be sufficiently long for the hatching of embryos of Trichocephalus and Ascaris—*i.e.*, for the fulfilment of the conditions necessary for infection.

It is a well known fact that human fæces may contain not only intestinal worms and their ova, but are also frequently the source of infectious microbes, such as the bacilli of typhoid fever, of dysentery, of tuberculosis, cholera vibriones, and others. I need only remind you of the story related in my first lecture of the Strassburg bakeress who carried typhoid bacilli about with her and infected her employés by means of her fæces. As an example of contagion with cholera, I may mention a case communicated to me by Dr. Ruffer, of Alexandria. During the last cholera epidemic in Egypt one of the victims of the disease was an old lady who had been suffering from an intestinal disorder, and who never took raw food. Her nourishment consisted exclusively of beef-tea. Researches made with a view to finding an explanation for the

mysterious origin of the disease proved that the patient must have become infected through the broth prepared by the cook, who had been suffering from a slight attack of diarrhœa. The broth was drunk cool during the hot season, and was served by this servant, whose hands had been soiled by his fæces, which contained quantities of spirilla. Thus we here see a case of infection of the mistress by the fæces of the servant, a case which we have selected from a great number of analogous ones.

The discovery that persons enjoying perfect health often harbour infectious germs dangerous to their surroundings has caused rather a disturbance in the rules of hygiene. Formerly examinations were mainly carried out on patients, as they were believed to be the principal source of contagion. Their beds, their linen—in short, everything that had come within their reach—was disinfected, but no attention was paid to the persons who were feeling well. At present efforts are directed to find out among the latter class of people the "bacilli carriers," so as to bring to bear on them the precepts of hygiene. To this end bacteriological laboratories are founded,

amongst which are the very admirable ones of The Royal Institute of Public Health, in which examinations of excreta of patients and of healthy persons are carried out. As soon as a carrier of pathogenic microbes has been discovered, the attempt is made to isolate him until he becomes harmless: at the same time his contagious dejecta are disinfected. In practice this method is fraught with great difficulties, as has recently been stated by Klinger of Strassburg. The ideal—to transform every w.c. into a bacteriological laboratory—can evidently never be attained. The disinfection of the excreta, which may occasionally contain pathogenic microbes for several years, is equally impracticable on a large scale.

It is evident that hygienic measures destined to prevent contamination of the digestive apparatus must, in the first place, watch over everything that enters it by the mouth. Food and drink should at least be boiled before being consumed. The temperature of boiling is insufficient for sterilization—there always remain spores of *Bacillus subtilis* and some others—but the ova of parasites and the pathogenic microbes will be destroyed almost without exception.

The prejudice that boiled water tastes bad and is unwholesome is very widely spread. This idea is most assuredly false; if water is boiled in a perfectly clean vessel it has no disagreeable taste whatever. An Italian scientist has carried out the following experiment: he filled several glasses with boiled water and an equal number with unboiled water of the same origin. Persons asked to taste the water were unable to distinguish the two lots from one another, so slight is the difference between raw and boiled water. I have myself found that boiled water is in every respect most satisfactory, and have drunk no other water for about ten years.

Still greater have been the objections brought forward against the boiling of milk. It is believed that boiled milk is less easily digested, and that in consequence of the destruction of certain diastatic substances it loses many of its qualities. Nevertheless, it is an established fact that a very large number of infants are reared with boiled milk, and that—provided sufficient care is taken to keep their feeding-bottle or feeding-spoon clean—the results of this method of rearing are excellent. Occasionally boiled milk may cause disorders of digestion,

and then it should be replaced by raw milk, but such cases are rare, and more than counterbalanced by those in which boiled milk is preferable to raw. In October last there was held at Paris an International Congress of the "Goutte de lait," at which many of the most competent pædiatric authorities were present. A great number of results were communicated, which would leave no doubt as to the value of feeding infants with boiled milk. Where pasteurization of the milk—*i.e.*, heating to between 65° and 70° C.—is practicable, it may well replace the process of boiling.

The process of boiling should also be extended to vegetables. As it cannot be doubted that especially salad, radishes, and other raw vegetables transmit entozoa and pathogenic microbes, their surveillance, therefore, from a hygienic point of view becomes indispensable. Washing these vegetables, even with boiled water, is not sufficient, and it is necessary at least to scald them with boiling water, or, better still, to boil them like salads.

Among fruits it is principally strawberries which introduce parasites, ova and infectious germs into the intestinal canal. It is therefore necessary to boil them. Even cherries,

although growing on trees and far from the soil, should be carefully scalded or boiled, because the birds which take a bite out of them frequently contaminate them with contagious matter. It is as a rule wiser to eat fruits, so far as possible, in the form of jams or compôtes.

With regard to animal foods, there are but few which are eaten raw. The danger of oysters has frequently been alluded to, and their rôle in the etiology of some cases of typhoid can no more appear doubtful.

The public is also sufficiently enlightened on the possibility of contracting tape-worm disease from insufficiently boiled beef, veal, pork, and certain fresh-water fishes, so that I need not here insist on this subject. Yet it happens quite often that doctors prescribe raw or very under-done meat to such of their patients whose weak state of health is caused by the growth of tæniæ. But such examples of neglect of hygienic rules are becoming far more rare than formerly. An idea is prevalent not only among the general public, but even among medical men, that raw or boiled eggs are an excellent food-stuff. But it is forgotten that the white of egg, which is elaborated in

the oviduct, in the immediate vicinity of the cloaca, often contains microbes, and occasionally even entozoa. There can be no doubt that the whipped cream of pastries, which sometimes causes very serious illness, owes its harmfulness to raw or insufficiently boiled white of egg.

Not only is it most desirable to take no food that has not been heated up to between 65° and 100° C., or even higher, but it is often, especially at times of epidemics of cholera or other intestinal diseases, necessary to make sure that the food has not been touched by suspicious hands. To that end it is desirable to provide dishes heated by spirit-lamps, on which the food should be placed before consumption.

The precautions suggested by me might at first sight appear difficult to be carried out in reality. Nevertheless, I can testify to the fact that, once one has got accustomed to them, they enter into practice without any difficulty. Many persons believe that raw food is indispensable to health. Charrin has published several Papers in which he seeks to prove that rabbits reared with sterilized food develop less satisfactorily and die more often than rabbits that

have been fed in the ordinary way. Without intending to enter into a discussion of Charrin's arguments, and even although I accept the results of his experiments as unassailable, yet we must not lose sight of the fact that these experiments apply to rabbits—*i.e.*, to herbivores—which have to utilize the cellulose of their food. Now, cellulose cannot be digested without the aid of microbial ferments, which naturally are rarer in rabbits fed with sterilized foodstuffs. To man, however, we ought under no circumstances to extend the results of these experiments.

Ch. Richet has, a short time ago, emphatically stated the fact that dogs, if brought up on raw meat, far more rapidly make up for any losses, and show a higher resistance towards tuberculosis than dogs which have been fed with boiled food. Now, this argument might apply to human food, and must therefore be considered. Also, occasionally the bacterial contents of raw milk may present real advantages to the consumer.

Having regard to these facts, we might give the general public a chance of eating raw food, provided that it is free from any danger to the consumer. It would therefore be worth while

to apply the principles suggested by Hempel, Wilhelms, and others to the obtaining of aseptic milk. It is only the difficulties attendant on these methods which militate against the more general consumption of raw milk.

With regard to meat from butchers' shops, the use of mutton which has been boiled only superficially and not inside amply meets all wants.

One might arrange for vegetables and strawberries to be grown under satisfactory hygienic conditions, so as to permit of their being consumed raw. To that end it would be necessary to watch scrupulously over the soil and the manure, and to use only irreproachable water for the purpose of watering. Amongst the different varieties of strawberries the one called "Capronel" might be very serviceable, for it grows so high that its berries do not touch the ground, besides being noticeable for its peculiarly fine flavour and smell.

In future, when hygiene will have become more of a general habit to us, there will no longer be any need to insist on the use of sufficiently boiled food. But at present it is imperative for persons who want to carry out the precepts of hygiene to boil what they

drink and adequately to cook their solid food. This is the only way to prevent the entrance into our digestive apparatus of harmful microbes and of parasites which open up for these microbes a mode of entry.

No one can deny that a system based on the principles above laid down will insure the body against all sorts of diseases of the digestive apparatus. Possibly it might even assist us at the same time to avoid certain maladies, against which the science of to-day is almost entirely helpless.

It is a striking fact that, although certain infectious diseases, such as human plague and leprosy, are becoming more and more rare, others are raging with ever-increasing frequency. Amongst these I should mention appendicitis and cancer. These two diseases have also another fact in common—viz., that they are very often observed among the well-to-do and even the rich classes. Might there not be some cause common to both maladies which could explain the parallelism in their increase?

As we have shown above, the intestinal worms play an important part in the etiology of appendicitis, by allowing pathogenic

microbes to find their way into the mucous membrane. Now, these worms are most often introduced by raw food, amongst which vegetables and certain fruits are of primary importance. The progress attained in the cultivation of these plants has led to their increasing consumption. Only at a comparatively recent date strawberries and some vegetables, such as lettuce, came into such general use that they could be procured all the year round. Under these circumstances the frequency of intestinal worms, which do not even spare the teacher of hygiene, is easily explained.

We have mentioned above some facts showing the relations between entozoa and tumours. Might not the entozoa serve as gates of entry for the hypothetical parasites of these tumours? When treating of malignant tumours, we cannot limit ourselves to the domain of precise facts, as we do not at present possess any—at least, as far as concerns etiology. But when one has recourse to hypothesis, one can hardly avoid considering the possibility of their infectious nature. Note those tumours of mice which are so frequent in some localities, so rare in others.

Though they are but slightly virulent at the beginning, their virulence increases in proportion to the number of their passages through the bodies of rodents, as has been shown by Ehrlich.[1] The varieties which are not virulent enough to transmit cancer produce immunity towards the more virulent ones. These tumours, therefore, behave like infectious diseases, so that we may be allowed to infer that, although they require a propitious medium for their development in the body they yet originate in some germ imported from outside. Thus, in order to be introduced, these germs might use as intermediaries some objects which find their way into the human body without having been disinfected.

Whilst the malignant tumours on the whole are becoming ever more frequent, certain varieties of cancer are observed more rarely than formerly. Thus, according to Czerny,[2] amongst those classes which observe care in the cleanliness of their skin cancer of the skin is observed only in quite exceptional cases, and it has without a doubt become much rarer. By reason of this fact Czerny recommends as

[1] *Deutsche Mediz. Wochenschrift*, March 22, 1906.
[2] *Medicinische Klinik*, 1905, Nos. 17, 20, 22.

means of preservation against cancer rigorous cleanliness, and perhaps also the giving up of all raw food. I am the more ready to fall in with the proposals of this great German surgeon, as I myself have for many years carried out the system of cooked food, in the hope of thus avoiding this terrible disease.

For a long time the principle has been laid down that in the feeding of infants the use of raw food should be avoided. This principle is suitable for every time of life, and there is no reason why it should not be applied to adults and to aged people. Thus, we may avoid as far as possible the entry into the body of the causes of all kinds of diseases. But there exists yet another means of attaining this end. It consists in modifying the flora of our alimentary canal by acclimatizing to our intestine useful microbes. The first step in this direction has, I think, been taken during the last few years.

Amongst the useful bacteria the place of honour should be reserved to the lactic bacilli. They produce lactic acid, and thus prevent the development of butyric and putrefactive ferments, which we should regard as some of our

redoubtable enemies. It has been shown by an extensive series of experiments, which I cannot here treat of in detail, that certain lactic ferments easily accustom themselves to live in our intestines, and thus produce a beneficial influence. They prevent putrefaction, and thus diminish the excretion of sulphonic acid esthers. These same ferments help to regulate the functions of our intestine and kidneys, rendering valuable service to the entire body.

One can take such carefully-selected lactic ferments either in milk that has become acid under their influence or in the form of a powder or compressed tabloids. Dr. Tissier[1] employs them in the treatment of the various intestinal troubles occurring at any age. To this end he advises the use of cultures of lactic microbes made in lactose peptone water.

As putrefaction in the alimentary canal represents one of the causes of the general wear and tear of the human body, it was only natural to suggest the method that I have just referred to as a means of combating it. This method may now be summed up in a few words. It consists in the consumption of food-

[1] *Tribune Médicale*, 1906, p. 117.

stuffs not contaminated with microbes of entozoa, and in the introduction into our alimentary canal of an artificially-cultivated bacterial flora, foremost among which are the lactic acid microbes.

III.

HYGIENIC MEASURES AGAINST SYPHILIS.

Since it has been shown to be possible to guard both our skin and our alimentary canal against the attacks of insects and of entozoa conveying the virus of disease, it might have been fairly assumed that it would be far easier to protect man from the virus transmissible from one member of the human race to another. Flies and mosquitoes flit freely around us, it being often difficult to avoid or to seize them, but they can sting even through the clothes. The ova and larvæ of intestinal worms find their way into the human body most frequently through the channels of our food and drink. And yet, in spite of these many difficulties, it is possible to eliminate the danger of contamination by the viruses which accompany these lower animals.

How, then, does it happen that man runs a greater risk of being infected by a virus existing in other men? Man is the principal source of contagion in tuberculosis, influenza, and many other diseases of the respiratory organs. Man, again, carries about and communicates, without intermediary, the virus of venereal diseases. Since, then, both the organism which furnishes and the one which receives this virus belong to the human class, and are beings provided with the power of sense and of reasoning, it might appear simple and easy to avoid all danger. But in reality it is not so. Venereal diseases are widely spread wherever man lives, and this is true not only of the less formidable diseases, but also of the most dangerous one. Without mentioning some races with little or no civilization, such as the Siamese, amongst whom persons not tainted by this malady are considered as rarities, the disease is yet very common in those countries which have attained the highest degree of civilization. Thus, according to Dr. Lenoir,[1] in Paris, "among 100 men at least 13 to 16 infected individuals may be

[1] *Quoted from Fournier, "Prophylaxie de la Syphilis," Paris, 1903, p. 475.*

counted." It is mainly the young people who pay the greatest tribute to the disease. Soldiers and sailors, selected as they are from among the hardiest of the nation, suffer from it most frequently.

At the meeting of the British Medical Association[1] in 1899, many physicians, especially Mahon and Dick, called attention to the increase of syphilis in the English army. The number of days on which soldiers were incapacitated from duty on account of syphilis has become nearly trebled during the years from 1880 to 1897, whilst the number of men has only been doubled in that period. The greatest increase observed was in the number of secondary lesions. At Netley Hospital in 1897 about one-third of all the patients were suffering from venereal diseases, the number of which showed an increase of 15 per cent. in fifteen years.

It is useless to insist here on the great frequency of syphilis among those persons in whom it is, if I may use the term, a professional disease, for everyone is sufficiently well informed on that head. But I think it may be worth while to call your attention to the great

[1] "*British Medical Journal*," *August* 12, 1899.

number of cases of non-venereal syphilis. In some countries where the precepts of hygiene are hardly at all observed, the inhabitants of which live in a most extraordinary promiscuity, infections are of very common occurrence. In such cases syphilis chiefly attacks the children. In this respect the syphilis of the rural population of Russia presents features of special interest.

The following is the description given by the well-known syphilogist, Tarnovsky[1]: "By spreading mainly—in over 70 per cent. of the cases—by extragenital infection, syphilis in the rural districts often remains untreated for ten or more years, by reason of purely local conditions: thus it is transmitted to the descendants in the guise of different varieties of hereditary syphilis, beginning with fœtal and ending by late hereditary syphilis, with its parasyphilitic symptoms and degeneracy.

"In Western Europe we see syphilis localized mainly in the large cities, and spreading principally among the youth of the cultured classes. On the other hand, rural syphilis in Russia is, first and foremost, a

[1] *Comptes Rendus du XII. Congrès Internat. de Médecine*, Moscow, 1899, vol., iv., p. 8.

syphilis of the innocent, and spreads far more generally throughout the mass of the people, without distinctions of age or sex. The infant soon after its birth is often infected by a kiss from one of its parents who has contracted the infection. The grandparents may, in like manner acquire the disease by eating from the same vessels or by drinking out of the same glasses.

"The promiscuity, the indigence, and, above all, the ignorance of the rural population, as well as the entire absence of sanitary measures, are the reasons for the ever increasing spread of the contagion. After penetrating into an obscure hamlet thirty or sixty miles away from the habitation of a doctor, the disease not unnaturally establishes itself at every hearth, and spares none. Never is this terrible dissemination brought about by prostitutes, but most commonly by the little children who, by their games and their caresses, sow the infection broadcast."

No one will doubt the great frequency of syphilis. But there are many, even among the medical profession, who do not believe that the disease has a great influence on mortality. They say that it is amenable to treatment, and that syphilitic persons may live long.

It is quite true that syphilis by itself is not a fatal disease. In so-called malignant syphilis there evidently exists some secondary infection, which becomes generalized and is fatal through septicæmia. Yet, in spite of this, syphilis is one of the most important causes in shortening human life and in bringing about mortal diseases.

In the present state of our knowledge it is not easy to treat of this question accurately. Nevertheless, some well established data help us to come to a pretty correct idea about it. The best statements on this subject which I have been able to obtain have been furnished by Professor Runeberg,[1] of Helsingfors. In order to throw light on this subject, he studied the documents collected by the Insurance Society, of Kaleva, and further supplemented these documents by enquiries addressed to the physicians who had charge of the persons to whom the documents referred. Runeberg has collected altogether 734 cases of death which occurred in insured persons during a period of twenty-two years (1875-1897). He has proved that 84 of them—*i.e.*, over 11 per cent.—were due to diseases resulting from syphilis. Fore-

[1] *Deutsche Med. Wochenschrift*, 1900. pp. 297, 312, 329.

most amongst these diseases stood various affections of the heart (31 deaths), the relation of which to syphilis has been accepted by all—and which is not to be wondered at, seeing that the syphilitic virus establishes itself by preference in the vascular system. Then followed general paralysis with 22 cases. Nearly the same number of deaths (21) was caused by the other diseases of the nervous system, as, for instance, softening of the brain and apoplexy. There remained only a small number of cases, related to other affections, such as chronic nephritis (3), aneurysm of the aorta (2), arteriosclerosis (2), caries of the bone (1), cirrhosis of one lung (1), and tumour of the neck (1).

Since it is very probable that the deaths caused by cerebral apoplexy in persons under fifty years of age, as well as those resulting from syncope in persons of the same age, are the result of lesions primarily syphilitic, Runeberg adds to the 84 deaths mentioned above 28 further deaths, thus obtaining a mortality of 15 per cent., as the result of syphilis. Even this figure would, according to this observer, appear to be below the mark.

Among the other diseases that caused the

death of insured persons stands foremost tuberculosis, with a mortality of 21 per cent., whilst pneumonia follows, as third, with 10 per cent. Thus we receive confirmation of the general opinion that, next to tuberculosis, syphilis plays the most important rôle in the death-rate of persons whose lives have been insured—*i.e.*, of the most vigorous part of the population.

For a long time the dread of syphilis has been general, and frequent are the cases in which victims of this disease have committed suicide. This fear is caused partly by the prospect of disfigurement by tertiary lesions, partly by the dread of becoming a source of infection to their fellow-creatures. Yet suitable treatment and hygienic precautions may to a great extent lessen this evil, for tertiary syphilis is rare amongst persons who have received proper treatment. It is the fear of the numerous diseases following in the train of syphilis which renders life unbearable to the persons who have acquired it. Even according to the most optimistic calculations of Professor A. Fournier, serious treatment did not prevent general paralysis occurring in 5 per cent., nor did it prevent tabes developing in 4·4 per cent.

If you add to that the diseases of the heart and blood-vessels, leucoplacia buccalis, with cancer of the tongue, and many other grave affections, and if you take into account the dangers of antisyphilitic treatment in tuberculous and other debilitated individuals, you will agree that the fear of acquiring syphilis is most truly justified.

Small wonder, therefore, that under these circumstances, although the specific treatment of syphilis is one of the most effective in the whole arsenal of therapeutics, on all sides search is being made for some means of preventing infection! Many suggestions have already been made, and new proposals are almost daily being brought out for checking the progress of syphilis. It has been advised that the system of teaching should be altered, and that our customs be modified. Even new laws have been proposed.

It has been said that syphilis spreads, above all, because the young folk are ignorant of the great danger that they are running into, and that therefore they should be taught, young boys and girls being given some ideas relative to venereal diseases, whilst more detailed information on the question might be given in

the higher grade schools. But the answer to these suggestions has been that this reform would give rise to many objections without being sufficiently effective; for we all know that, in spite of having been adequately warned, young doctors and students of medicine furnish a large proportion of victims. Ignorance is therefore not the only cause.

As one of the strongest measures against syphilis, early marriages have been recommended. Young people should, it is said, marry early, so as to escape infection. But it is rarely possible for young men to marry before having finished their course of studies. Now, it is well known that syphilis is found only too often in scholars of the public and high schools, as well as in young girls who have not come of age. According to the data published by Ed. Fournier,[1] among 10,000 cases of syphilis in men contracted by venereal infection, 1,512, or more than 15 per cent., occurred in youths between eleven and twenty-one years of age. Of the 1,000 cases of syphilis in women collected in Fournier's table, the maximum (104 cases) was observed in girls

[1] *Professor A. Fournier:* "*Prophylaxie de la Syphilis,*" 1903, *pp.* 443-464.

of twenty years; altogether 313 women—*i.e.*, more than one-third—had not yet come of age. The figures just mentioned apply to private practice. The syphilitic patients seen in hospital practice acquire the disease even earlier, a fact which leads Fournier to the following conclusions: Men become infected "with syphilis at an earlier age in the lower than in the middle classes, chiefly at seventeen, eighteen, nineteen and twenty years. On the other hand, the greatest incidence among townsmen is observed between the twenty-first and twenty-ninth year." "Amongst the women of the people the great incidence in young individuals occurs at an earlier date than amongst women of the middle and upper classes. A rapid increase in incidence takes place between the sixteenth and seventeenth year, and continues up to about the twenty-second year. Amongst women of the rural population the incidence in youth reaches its summit at the eighteenth year, whilst in townswomen it occurs at the twentieth year" (p. 450).

According to these data one would have to advise the marriage of minors, which is contrary to the principle of evolution. More than thirty years ago I collected a great amount of

evidence on the age at which marriage was effected. The result of it was to show that this age has constantly risen, corresponding to the degree of civilization. Among savage or hardly civilized races marriage takes place far earlier than among highly civilized nations, and among the latter the age at marriage shows a steady increase. In order to change this state of things one would have to alter the progress of civilization. It would become necessary that young folks should marry and bring up their children at an age when they themselves have not finished their studies and have not yet obtained remunerative employment. In my own circle I am acquainted with some such early marriages. They have all ended in divorce or separation, for these young people at the time of marriage had not acquired any proper knowledge of life. I will not enter into a detailed discussion of this question, but will only state that to my mind the principle of marrying young as a safeguard against venereal infection cannot be regarded as practicable.

Nor can I go fully into the much debated question of regulation or abolitionism in the fight against venereal diseases. Great Britain,

so proud and jealous of her liberties, pushes this liberty to such a point that facilities are afforded for the communication of these diseases. Abolitionism originated on English soil, and from thence spread to other countries. There can be no doubt that the regulation of prostitution is a very imperfect procedure. Nor can there be any doubt that the restriction of liberty is most disagreeable and vexatious. Nevertheless, until a new order of things, regulation, even though partial and imperfect, is better than unlimited freedom. Assuredly it would be a great step forward if some method were discovered which made regulation and all intervention of public authorities superfluous, and thus insured mankind against syphilis by practical and simple means, dependent only on the will of those risking contagion. Endeavours directed to this end have not been wanting. Hardly a year has elapsed in which some vaccination, sero-prophylactic, or other individually preventive method against syphilis has not been announced.

Soon after the discovery of the main facts about the preventive action of sera, attempts were made to find an antisyphilitic serum.

Richet and Héricourt, who were the first to discover the efficacy of defibrinated blood in the prophylaxis of infectious diseases, tried to combat syphilis by this method. Their endeavours have failed, and in like manner also a great number of other attempts made in later years.

It would be useless for me here to enter into a discussion of this subject, the more so since any conclusions we could draw from it would be anything but encouraging. I will only mention the results of experiments carried out by Professor Roux and myself at the Pasteur Institute. We endeavoured, by different procedures, to obtain an antisyphilitic serum which would prevent the outbreak of the disease. We began by working on the lower monkeys, which, after recovering from their primary lesions, were subjected to subcutaneous injections of blood from patients with fully-developed secondary skin lesions. The serum of some of these monkeys showed a certain preventive action, but only if mixed with the virus before inoculation. If the serum were injected at a different spot from that used for the virus, the monkeys developed secondary symptoms of the same intensity as the control

animals; under these conditions, therefore, the serum showed no protective action whatever. Nor has the intravenous injection of syphilitic blood, practised on monkeys, brought us any nearer to the solution of the problem. We did not find it easy to make a large number of intravenous injections in the lower monkeys; and even though we operated also on the baboon, one of the largest of this monkey tribe, the result was not satisfactory. The baboon lost flesh considerably after several injections, and furnished only a serum of low efficiency.

No better effects were obtained with the serum of a goat, to which we injected, in the course of eight months, a quantity of syphilitic products from new-born infants that had died of hereditary syphilis. The serum of this goat did not even show any protective action when mixed *in vitro* with the virus; the result was, therefore, even inferior to that obtained with the serum of the monkey.

Perhaps the low efficiency of the sera employed by us may have been caused by our having injected insufficient quantities of virus into the body of the animals used in our experiments—viz., monkeys and goat. The

injection of greater quantities of syphilitic virus would, no doubt, have given better results. The discovery, made by Schaudinn, of a spirillum which ought certainly to be considered as the causal agent of syphilis lends further force to this hope; but unfortunately this microbe belongs to a group which cannot be cultivated on the artificial culture media hitherto employed. We shall, therefore, have to make much more progress before we can hope to obtain a practicable method of cultivating the syphilis spirillum on a large scale. In many institutes and bacteriological laboratories work is being carried on in this direction. Levaditi, of the Pasteur Institute, has taken the first step forward on this road by cultivating, not the spirillum of Schaudinn, but two analogous spirilla—namely, those of fowl septicæmia and of relapsing fever. He obtained a growth of these microbes in collodium sacs filled with coagulated serum, which he introduced into the peritoneal cavity of rabbits.

His results mark the beginning of a large series of experiments that will have to be made. We have the less reason to enlarge on these experiments, as the prophylaxis of syphilis will probably not be discovered by the sero-thera-

peutic method. Sera may be of great use in preventing epidemic diseases, such as diphtheria or plague, or accidental diseases—as tetanus. In these cases no difficulty is experienced in the injection of serum to persons exposed to the risk of infection. With syphilis the case is different, as the injections would have to be repeated very often.

A mode of prevention by means of vaccines, strictly speaking—*i.e.*, by means of attenuated virus, or by products of the virus—might possibly have a better chance of success, only in the search for these products the same difficulties are met with as in the preparation of an efficient serum. In order to transform a virus into a vaccine, by treating it with chemical substances, or by subjecting it to physical agencies, it is essential to possess larger quantities of it than are present in the syphilitic matter of chancres, of the inner organs or the blood. We must, therefore, wait or the time when we shall possess cultures of the syphilis spirillum. For the time being it is of no use entering into the question of antisyphilitic vaccines.

With reference to this subject, I must mention an experiment carried out in 1903 by

Roux. A chimpanzee that had been inoculated with the virus from a primary lesion of a macacus (*Macacus sinicus*) showed only insignificant lesions at the spot of inoculation; and yet the same chimpanzee, after being re-inoculated at a later period with the virus of human origin, proved refractory. In the further course of this experiment the only symptom observed by us that could be attributed to syphilis was a general swelling of the lymphatic glands. We published these facts at the time, and interpreted them as a proof of an attenuation of the syphilitic virus being effected by the body of the macacus, since we considered that this might be of importance in the search for methods of vaccination. Later on we commenced studying the properties of the virus after it had been modified by the body of a lower monkey. We found that a virus which had been passed through a Javanese macacus (*Macacus cynomolgus*), or a baboon, (*Cynocephalus sphinx*), caused primary and secondary syphilitic lesions in the chimpanzee, which were just as typical as those which occur in man. Following the suggestion made to us by Finger and Landsteiner, of Vienna, we inoculated chimpanzees

with virus which had been passed through the *Cynocephalus hamadryas* and the *Macacus rhesus*. One chimpanzee, after inoculation with the eleventh passage of hamadryas, presented a most typical primary lesion. The chancre was well developed, and accompanied by a marked swelling of the regional lymphatic glands. Another chimpanzee, inoculated with virus from the eighth and ninth passages of the rhesus, also showed a very well-developed primary affection, and some suspicious lesions on its head and back.

The primary lesions in these two cases, in which chimpanzees were tested with virus passed repeatedly through the body of lower monkeys, were far more pronounced than those which we had observed in the chimpanzee inoculated with the virus of *Macacus sinicus*. In spite of this difference, some facts indicated that a certain attenuation of the virus had been attained in the rhesus. The monkey of the ninth passage already presented only a slight lesion. Endeavours undertaken both in Vienna and in Paris to keep new passages going in the rhesus were unsuccessful, so that in order to preserve the virus it became necessary to employ the chimpanzee. Thus

the primary lesion of this anthropoid ape which developed after inoculation of the eighth and ninth passage through the rhesus appeared to be virulent for other individuals of this species of monkey. In this way we obtained three new passages of the same virus.

The facts which I have just placed before you indicate, firstly, that the virus of *Macacus rhesus* is attenuated by several passages, so as at last to lose its virulence for this species of monkey; secondly, that the chimpanzee may strengthen this weakened virus.

Since the zoological distance between the macacus and man is greater than that between the macacus and the chimpanzee, one might suppose that the virus of the macacus would act on man differently to the chimpanzee. A chance occurrence has just thrown some light on this problem. One of our laboratory assistants who took an active part in our experiments, and who frequently handled the syphilis infected monkeys, one day noticed an ulcer on his lower lip, which appeared suspicious to him. However, since the lesion was not accompanied by any swelling of the lymphatic glands, and since it healed soon after its appearance, it was forgotten for the

time being. Not until a month later, when Dr. L—— noticed on the same lip an ulcer similar to the first, did he think it necessary to apply for medical advice. Yet again there was no swelling in the lymphatic glands, and as the lesion on the lip appeared to be superficial and insignificant, there was thought to be no reason to consider it as a syphilitic affection, but in order to be quite sure, a Javanese macacus (*Macacus cynomolgus*) was inoculated with some fluid drawn from the small ulcer.

Great was our astonishment when, four weeks after the inoculation, two most typical primary lesions were observed on the eyebrows of the macacus. All doubts ceased of their true nature when these lesions of the monkey were found to be teeming with Schaudinn's spirilla.

Our assistant, made anxious by this discovery, consulted the greatest living authority on syphilis, Professor Fournier, so as to ascertain whether mercurial treatment would be necessary. After a most thorough examination, this eminent savant emphatically denied any such necessity. He found nothing justifying the diagnosis of syphilis, and advised no treatment to be undertaken. The non-occurrence of any, even the

slightest, suspicious symptoms in the space of six months justified Professor Fournier's advice. Clinically our assistant did not suffer from syphilis, and yet the ulcer on his lip caused an absolutely characteristic primary lesion in the macacus.

An explanation of this most contradictory result can only be given by assuming that Dr. L—— had, through some carelessness, got his mouth infected with virus from a macacus, which acted on him like a very attenuated virus. The hypothesis of a former syphilis, which might have explained the slightness of the lesion following an accidental reinfection, must be absolutely excluded, for Dr. L—— has never had syphilis.

It will be understood that, after obtaining these data, we consented to the inoculation of a human being with virus passed through a macacus. From a number of persons who had repeatedly begged us to try the effect of antisyphilitic vaccination on them, we selected an aged person, who affirmed that she had never had syphilis, and who offered herself of her own free will to an experiment of this kind. The most minute examination justified this assertion. The virus, which had been passed

through a *Macacus sinicus*, was inoculated on three different parts of her forearm. After an incubation period of twelve days, there appeared two small non-ulcerated pustules of a reddish-brown colour, which resembled the pustules of secondary syphilis. After several weeks they disappeared, leaving only two pigmented spots. As in the case of Dr. L——, neither any swelling of the lymphatic glands nor any other secondary lesion has been observed during more than half a year.

Such are the facts which lead us to believe that the macaci may attenuate the syphilitic virus for their own species and for man. These facts, of course, give us only a first indication, and we are still far from possessing a method of antisyphilitic vaccination. Even if, at a later stage, the existence of a vaccine against syphilis were conclusively proved, it could only be employed under very exceptional conditions. The attenuated, and therefore living, virus, might, in fact, bring about most awkward complications if used on a large scale. Do we not know that some of the patients suffering from general paralysis and from tabes have only shown quite insignificant syphilitic lesions? Only to those persons who are exposed to the

greatest risk of acquiring human syphilis could one propose vaccination with an attenuated virus. In point of fact, the hypothesis that this vaccine might provoke more serious complications than true human syphilis is not admissible; at any rate, it is not based on any scientific data.

The persons liable to benefit from vaccination would at first have to be selected from among the beginners in prostitution. It is an established fact that these women only in exceptional cases escape syphilis. As almost all of them are, therefore, most liable to acquire this disease, vaccination would be an advantage for them, as well as for the men having intercourse with them; but in practice the carrying out of this proposal meets with serious difficulties, since the beginners in prostitution are very young, and almost always minors. According to the data collected by E. Fournier,[1] syphilitic infection in prostitutes "begins early—*i.e.*, it is first observed about the fourteenth year." Syphilitic infection afterwards shows a speedy increase in frequency among these girls, especially between their fifteenth and seventeenth year, and attains its maximum in the

[1] *Professor Fournier*: "*Prophylaxie de la Syphilis*," *p.* 452.

eighteenth year. Being minors and withal ignorant, these young prostitutes enjoy full liberty, without the slightest constraint being put upon them. How could one persuade them to submit to be vaccinated against syphilis?

The conditions for such vaccination are very different in the cases of family syphilis, which I mentioned before when speaking of the frequent occurrence of the disease amongst the rural population of Russia. Children who are in danger of acquiring syphilis from their relatives, and who pass the disease on to other children, might more easily be subjected to vaccination. They have not the liberty to do as they like, and must obey their parents, and the chances are that the parents might more easily be brought to understand the advantage of such measures. Vaccination with a virus so attenuated as to cause no secondary lesions would contribute materially to the lessening of the evil. The vaccine might be inoculated into those parts of the body which are least exposed to contact—*e.g.*, the forearms. The possibility of the primary lesion causing infection would thus be reduced to a minimum, whilst the chances of contamination by a kiss or other dangerous contact with persons suffering from

"plaques muqueuses" would be entirely removed.

Thanks to the facilities for studying this question by experiments on monkeys, the solution of the problem of antisyphilitic vaccination need no more be regarded in the light of an unrealizable and Utopian scheme. Central laboratories for the preparation of vaccines would have to be founded, in which attenuated vaccines could be maintained by alternate passage through anthropoid apes and lower monkeys. The latter, after having been proved to be free from tuberculosis by the tuberculin test, would furnish the necessary vaccines. Before, however, this method can be realized in practice, we have yet a long distance to traverse.

Whilst there will always be narrow limits to the prophylactic treatment of syphilis by means of living vaccines, the vaccination of persons suffering from hard chancre against the occurrence of secondary symptoms will be applicable on a large scale. In fact, a patient with a primary lesion is practically sure to develop secondary symptoms of syphilis. He would, therefore, risk nothing by the injection of any vaccine intended to prevent the outbreak of

these symptoms. The question remains whether such a vaccine can really be prepared. This is the idea of Kraus and Spitzer. They assumed that, in like manner as a person during the incubation period of hydrophobia may be saved by injections of the virus of rabies, a person who had acquired a syphilitic chancre might be protected against secondary lesions by subcutaneous injections of syphilitic virus. The first results obtained by them in patients appeared promising, but in course of time it was proved by Brandweiner and other syphilis specialists that injections carried out by Kraus' method could not prevent the development of secondary lesions. An experiment carried out on the chimpanzee also furnished a negative result.

In this state of affairs—*i.e.*, in the face of the difficulties at present besetting the plan of vaccination against primary and secondary syphilitic lesions—it was only natural to seek for some other means of prophylaxis against this terrible disease.

It being a generally established fact that mercury is a sovereign remedy for syphilis, Dr. Behrman,[1] of Nürnberg, six years ago,

[1] *Dermatologisches Centralblatt*, 1900, p. 172.

suggested inunction of gray mercurial ointment as a preventive measure. He advised rubbing the genital organs for several minutes with 3 to five grammes of the ointment. The first inunction should be carried out as soon as possible after the suspicious contact, and the treatment was to be repeated on the following day.

Dr. Cohn,[1] of Berlin, has suggested a modification of this method, which consisted in applying, before the contact takes place, a salve made up of Ledermann's mercurial preparation and resorcin. After contact he advised washing with mercurial soap.

To the same prophylactic end, Dr. Guiard,[2] of Paris, proposed yet another method—viz., washing with a solution of corrosive sublimate (1 : 4,000 or 5,000). He considered that if the prostitutes would but make use of this simple procedure, syphilis would spread far less than it does at present. Like the German physicians whom I have just quoted, Guiard bases his suggestion on the well-known therapeutic efficiency of mercury and its salts.

Since syphilis can be inoculated to catarrhinian

[1] *Dermatologisches Centralblatt*, 1900, p. 237.
[2] *Annales de Dermatologie et de Syphilographie*, 1901, p. 1037

and anthropoid apes as well as to lower monkeys, there was every reason for carrying out an experimental study of these questions of prophylaxis, and it is with this end in view that Professor Roux and I have been working.

A macacus was inoculated with syphilitic virus, and one hour afterwards treated at the seats of inoculation with a solution of sublimate (1 : 2,000). This did not prevent the development of a primary lesion. In the experiments carried out in Java by Neisser[1] and his assistants, injections of sublimate begun immediately after the inoculation of the syphilitic virus could prevent neither the development of a chancre at the seat of inoculation nor the general distribution of the virus throughout the body. Furthermore, one of the patients who furnished us with the virus had acquired the disease in spite of the habit of regularly washing himself with sublimate after every contact.

It is probable that washing with sublimate is not effective because its action is limited to the surface. Inunction with mercurial ointments is preferable, for by this method the mercury is absorbed in a far superior way.

In a long series of experiments carried out on

[1] *Deutsche Medizin, Wochenschrift*, 1906, p. 52.

chimpanzees, baboons and macaci, mercurial inunction successfully prevented the outbreak of a primary lesion. The virus was inoculated either on the eyebrows or on the genital organs of the males and females. It was taken from a primary lesion in man, and was thoroughly applied with a scarifier. The ointments employed were prepared either with metallic mercury or with calomel, white precipitate or salicyl-arsenite of mercury. The substances were suspended in lanoline (1 : 3 or 1 : 4). Inunction was carried out for four to five minutes, and was begun between one and twenty hours after the inoculation. Even when applied eighteen and a half hours after infection, calomel salve still proved effective.

The result of these experiments is that mercurial ointments may certainly be useful prophylactics against syphilis in all those cases where a contact, however little suspicious has taken place. Instead of gray ointment, which causes much irritation in the skin and mucous membranes, the use of salves made up with non-irritating mercury salts should be recommended—*e.g.*, calomel or the other salts already mentioned.

The results obtained on lower monkeys and

on anthropoid apes agreed so well as to justify the conclusion that the same method might also serve for the prevention of syphilis in man. Nevertheless, to make sure, we decided to try an experiment on man. We inoculated, at his own request, a young medical student who had almost completed his studies with virus from the chancres of two syphilitic men. An hour after, the parts inoculated were rubbed for five minutes with an ointment which contained in 3 parts 1 part of calomel. The young man, although certainly free from any former syphilitic taint, developed no primary lesion. Four macaci were treated with the same virus with which he was inoculated. Two of them, used as control animals, showed primiary lesions seventeen days later. A third macacus was rubbed with the calomel ointment an hour after inoculation of the virus, and remained free from any syphilitic lesion, like the young man. The fourth macacus was rubbed with the ointment twenty hours after inoculation, and showed a primary lesion after thirty-nine days.

The results of this experiment, therefore, permit us to conclude that man can with advantage employ mercurial ointments after every suspicious contact in order to preserve himself

from syphilis. The study of this prophylactic method is not yet finished. Perhaps even a less prolonged inunction with ointments containing a lower percentage of mercurial salts might successfully prevent the development of the virus. But these questions, as well as a certain number of other details, will only be cleared up by new experiments, which have already been begun.

There are not wanting persons who consider that every measure which is intended to limit syphilis only serves to encourage vice, and that it would be better to let the disease spread freely. I am not about to discuss the morality of those who acquire this evil by sexual intercourse; but are not many victims absolutely innocent, and have not they a right to be protected? Persons who look upon the prophylaxis of syphilis as immoral should apply the same reasoning to the use of antiseptics in midwifery, because it facilitates criminal abortion. And if this paradox were carried through to the bitter end, one might oppose not only the prophylaxis, but also any treatment of syphilis. Men of genius, tainted with syphilis, have produced remarkable work, in the creation of which the cerebral excitement caused by the

disease has, doubtless, played an important part. It is easy to recognise in Schumann, Nietzsche, and Guy de Maupassant the morbid influence of their general paralysis. Perhaps had they not had syphilis they might have produced fewer works of genius. And yet must we not regret that they used no prophylactic measures, and, even more, that they were not subjected to an energetic specific treatment?

No considerations of a moralizing tendency should be opposed to the prevention of so disastrous a calamity as syphilis. True morality ought rather to contribute as much as possible to the prophylaxis of this and many another disease.

Old fashioned ideas, which have become firmly rooted, condemn the care that one takes of one's own health. By such, one may care for others, whilst the taking of precautions for oneself is forbidden.

Ruined buildings and tattered clothing may appear more beautiful from an artist's point of view than complete houses and clean clothing, yet civilization tends ever more to replace the former by the latter. In questions of health, Morality should not attempt to lead Hygiene, but should rather follow her. Even in the

religions of old, hygienic precepts occupied an important place. With how much more reason ought not modern hygiene, having become an exact and infinitely more precise science than it was formerly, to reign supreme over all moralizing doctrines?